remarks is respectfully requested.

## I. Rejections under 35 U.S.C.§112, first paragraph

Claims 20-25 are rejected under 35 U.S.C.§112, first paragraph on the grounds that they contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention. The Examiner contends that the specification is not enabled for prevention of a disease or disorder associated with Alzheimer's Disease as no evidence shows complete avoidance of Alzheimer's Disease in all animals and cells.

This rejection is traversed, and reconsideration is respectfully requested.

Claim 20 is amended to recite "reducing the likelihood" rather than "prevention". In light of the amendment to claim 20, Applicants respectfully request withdrawal of this rejection.

## II. Rejections under 35 U.S.C.§ 112, second paragraph

Claims 8 and 16-17 are rejected under 35 U.S.C.§112, second paragraph as indefinite. The Examiner asserts that claims 8 and 16 require that the animal is ovariectomized and orchidectomized.

This rejection is traversed, and reconsideration is respectfully requested.

Claims 8 and 16 are amended to recite "gonadectomized" in place of "ovariectomized". In light of the amendment to claims 8 and 16, Applicants

respectfully request withdrawal of this rejection.

## III. Rejections under 35 U.S.C.§ 102(b)

Claims 1-3, 5-6, 20-21, and 23-25 are rejected as anticipated by Lee *et al.* (WO 98/43647). The Examiner concludes that claims 1-3, 5-6, 20-21 and 23-25 are directed to the mechanism of action of Lee *et al.* and are thus inherent in Lee *et al.*

The Examiner states that Lee *et al.* discloses administration of estrogenic compounds to reduce or maintain low levels of amyloid precursor protein (APP) for treatment of Alzheimer's Disease. The Examiner also states that Lee *et al.* discloses a method for determining the capacity of a drug to inhibit the expression, production or formation of APP in a cell comprising contacting an estrogenic drug with a cell culture that has the capacity to synthesize APP. The level of APP produced is then compared to a control (page 11, lines 20-29).

This rejection is traversed, and reconsideration is respectfully requested.

Claim 1 of the present invention recites the following:

> A method for reducing a level of amyloid- β (Aβ) peptides *in vivo,* which method comprises administering an Aβ level reducing dose of an estrogen compound to an animal, wherein the animal has an increased level of Aβ.

Lee *et al.* teach a method of reducing the level of APP *in vitro* using primary cultures

of rat cortical astrocytes and human glioma cells. Lee *et al.* does not teach reducing a level of amyloid-β *in vivo,* as recited in claim 1 above. Furthermore, the cell culture assays described in Lee *et al.* do not show the effect of an administered dose of estrogen on brain cells because such factors as absorption, transportation and metabolism of the drug may affect the *in vivo* effects of the drug on the brain. In order to anticipate a claim, "the identical invention must be shown in as complete detail as is contained in the . . . claim". *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1239 (Fed Cir. 1989). Lee *et al.* do not anticipate the present invention because no *in vivo* effects of an administered dose of estrogen are disclosed in the reference.

Furthermore, Lee *et al.* teach treating confluent monolayers primary rat cortical neurons and human glioma cells with doses of 1, 10, or 100 μM of lipophilic estrogenic compounds such as estrone or 17β-estradiol (see page 20, lines 24-27). The lowest molar concentration (1 μM) described by Lee *et al.* is 1000 times the maximum physiologically level employed in humans. The maximum physiological level of estradiol in humans is 8-10 nM. Therefore, the concentrations taught by Lee *et al.* are not realistic for treatment *in vivo* nor are they predictive of how a substantial (1000 times less) physiologically level of estradiol will affect the level of APP in brain cells *in vivo*. Since the concentrations of estradiol taught by Lee *et al.* are not realistic concentrations for *in vivo* use, the claims are not inherent in Lee *et al.*

Additionally, the Examiner has rejected claims 1-3, 5-6, 20-21, and 23-25

under 35 U.S.C. § 102(b) as anticipated by Lee *et al.* in combination with Borchelt *et al.* The Examiner relies on Borchelt *et al.* to support his conclusion of inherency. The Examiner admits that Lee *et al.* does not specifically teach a role for the ratio of Aβ42 toAβ40 in the pathogenesis of Alzheimer's Disease (see paragraph 11 of the office action). The Examiner relies on Borchelt *et al.* for disclosing a role for the ratio of Aβ42 to Aβ40 in the pathogenesis of Alzheimer's Disease.

This rejection is respectfully traversed, and reconsideration is requested.

The same arguments made above with respect to Lee *et al.* apply to this rejection also. Furthermore, Borchelt *et al.* do not make clear that the missing descriptive matter (the effect of estrogen on Aβ42 and Aβ40) is present in the matter described in Lee et al. "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746. 1749 (Fed. Cir. 1991). Accordingly, since Borchelt et al. does not disclose or suggest the effect of estrogen *in vivo* on Aβ42 and Aβ40, Borchelt *et al.* cannot be relied upon as a basis for inherency.

Borchelt *et al.* do not show a correlation between elevated Aβ42 and Aβ40 levels and abnormal APP synthesis or APP expression. Applicants draw the

Examiner's attention to Figure 2 (page 1007) and Table 1 (page 1008) of Borchelt *et al.* Figure 2 depicts APP expression in stable N2a cells. Table 1 shows the corresponding ratio of Aβ1-42(43)/Aβ1-40 species secreted by the stable N2a lines of Figure 2. Comparing the wild-type PS1 lines, .7 of Figure 2 correlates to a ratio of 0.093, .3 correlates to a ratio of 0.094, and .25 correlates to 0.1060. Comparing the $_{\Delta}$E lines, 9.23 correlates to a ratio of 0.137, 9.21 correlates to a ratio of 0.113, 9.9 correlates to a ratio of 0.199, 9.14 correlates to a ratio of 0.195, and 9.18 correlates to a ratio of 0.206. Comparing the data of Figure 2 with the data of Table 1 shows that Borchelt *et al.* do not show a correlation between APP expression and the ratio of Aβ peptides. Accordingly, Borchelt *et al.* do not make clear the missing matter in Lee *et al.*

## IV. Rejections under 35 U.S.C.§ 103

Claims 1-6, 15, and 18-30 are rejected as obvious over Lee *et al.* alone and further in combination with Borchelt *et al.* The Examiner concludes that it would have been obvious to one skilled in the art at the time of the invention to combine Lee *et al.* and Borchelt *et al.* to measure the amounts and/or ratio of Aβ42 to Aβ40 to determine whether a compound is effective at reducing these levels or ratio.

These rejections are respectfully traversed, and reconsideration is requested.

The same arguments made above with respect to Lee *et al.* and Borchelt

*et al.* apply to these rejections. Furthermore, neither reference contains any motivation to combine Lee et al. with Borchelt *et al.* Lee *et al.* only teaches lowering APP levels in brain cells cultured *in vitro* with astronomical levels of estradiol. Borchelt *et al.* show no correlation between APP expression and the ratio of Aβ42 to Aβ40. Borchelt *et al.* teach that familial Alzheimer's Disease-linked presenilin 1 variants elevate Aβ1-42/Aβ1-40 ratio *in vitro* and *in vivo*, not APP expression. As admitted by the Examiner, Lee *et al.* does not specifically teach a role for the ratio of Aβ42 to Aβ40 in the pathogenesis of Alzheimer's Disease. Since Lee *et al.* does not specifically teach a role for the ratio of Aβ42 tp Aβ40 in the pathogenesis of Alzheimer's Disease and Borchelt *et al.* does not provide a link between APP expression and the ratio of Aβ42 tp Aβ40 in the pathogenesis of Alzheimer's Disease, neither reference provides the needed motivation to combine the references.

Accordingly, Applicants respectfully request withdrawal of these rejections.

Claims 1-30 are rejected as obvious over Lee *et al.* in combination with Borchelt *et al* and in further combination with Simpkins *et al.* Claims directed to orchidectomy are further rejected in view of Williams and Stancel (Goodman and Gilman's 1996). The Examiner relies on Simpkins for teaching ovariectomy as a model for postmenopausal changes and Williams and Stancel for teaching the synthesis of estradiol from testosterone. The Examiner concludes that it would have been obvious to one skilled in the art at the time of the invention to combine Lee *et al.*, Borchelt *et*

*al.* and Simpkins to utilize ovariectomy as a model for postmenopause, and to determine the capacity of a drug to treat Alzheimer's Disease through measurement of amounts and/or ratios of Aβ42 to Aβ40.

Applicants respectfully traverse this rejection, and reconsideration is requested.

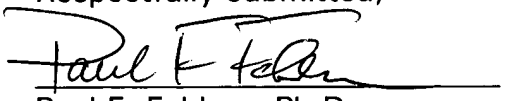
Our previous arguments regarding Lee *et al.* and Borchelt *et al.* apply to these further rejections. In light of our previous arguments, Simpkins et al. and Williams and Stancel do not suggest or disclose anything to fill in the necessary subject matter missing from Lee et al. and Borchet et al. to arrive at the present invention.

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the

Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Paul F. Fehlner, Ph.D.
Reg. No. 35,135
Attorney for Applicant(s)

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

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**MARK-UP FOR AMENDMENT**
**PURSUANT TO 37 C.F. R. § 1.121**

Hon. Commissioner of Patents
Washington, DC 20231

**IN THE CLAIMS**:

8. The method according to claim 7, wherein the animal is [an ovariectomized (ovx)] a gonadectomized animal.

16. The method according to claim 15, wherein the animal is [an ovariectomized (ovx)] a gonadectomized animal.

20. A method for delaying or [preventing the onset] reducing the likelihood of, or ameliorating, a disease or disorder associated with amyloidosis, which method comprises administering an Aβ level reducing dose of an estrogen compound to a subject who has an increased risk for developing or shows a symptom of the disease or disorder associated with amyloidosis.